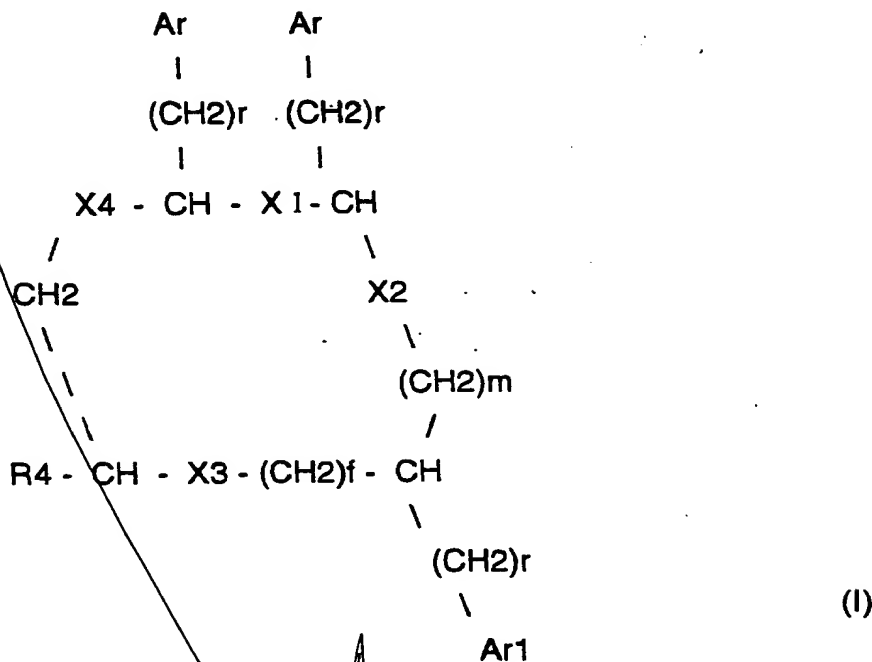


## CLAIMS

## 1. Monocyclic compounds of general formula (I)



wherein:

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, same or different, are a group chosen among: -CONR-, -NRCO-, -CH<sub>2</sub>-NR-, -NR-CH<sub>2</sub>- where R is H, C<sub>1</sub>-3 alkyl, benzyl;

f, m, same or different, are a number chosen among 0, 1 and 2;

R<sub>1</sub> and R<sub>2</sub>, same or different, represent a group:

-(CH<sub>2</sub>)<sub>r</sub>-Ar where r = 0, 1, 2 and Ar is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 substituents chosen among C<sub>1</sub>-3 alkyl, haloalkyl, C<sub>1</sub>-3 alkoxy, C<sub>2</sub>-4 amino-alkoxy, halogens, OH, NH<sub>2</sub>, CN, NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, same or different, are H or C<sub>1</sub>-3 alkyl,

R<sub>3</sub> is

(CH<sub>2</sub>)<sub>r</sub>-Ar<sub>1</sub> where r = 0, 1, 2 and Ar<sub>1</sub> is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 groups chosen among C<sub>1</sub>-3 alkyl and haloalkyl, C<sub>1</sub>-3 alkoxy and amino-alkoxy, NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, same or different, are H or C<sub>1</sub>-3 alkyl, -alkoxy, halogens, OH, NH<sub>2</sub>.

same or different, are H or C<sub>1-3</sub> alkyl,

R<sub>4</sub> is a group chosen among:

- NR<sub>8</sub>R<sub>9</sub>, where R<sub>8</sub> is H or C<sub>1-3</sub> alkyl and

R<sub>9</sub> is

- 5 (i) a methanesulfonyl, tosyl, tetrahydropyranyl,  
(ii) tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom,  
(iii) piperidyl possibly substituted on the N-atom by a C<sub>1-3</sub> alkyl, C<sub>1-3</sub> acyl, aminosulfonyl, methanesulfonyl;  
10 (iv) a group (CH<sub>2</sub>)<sub>g</sub>-R<sub>10</sub> where g is 1,2,3 and R<sub>10</sub> is chosen among morpholine, furan, CN;

or R<sub>8</sub> and R<sub>9</sub> together with the N atom to which they are linked form a piperazine possibly substituted on one of its nitrogen by a C<sub>1-3</sub> alkyl, C<sub>1-3</sub> acyl or methanesulfonyl;

- 15 N(R<sub>11</sub>)CO(CH<sub>2</sub>)<sub>h</sub>-R<sub>12</sub> where R<sub>11</sub> is H or C<sub>1-3</sub> alkyl; h is 0,1,2,3; and R<sub>12</sub> is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or hydroxymethyl, piperidine possibly substituted with a group hydroxy carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C<sub>1-3</sub> alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly  
20 mono or di-oxygenated on the S-atom, amino- cyclohexane possibly substituted by an hydroxy group.

- COR<sub>13</sub> wherein R<sub>13</sub> is a group chosen among morpholine and piperazine possibly substituted by a C<sub>2-6</sub> alkyl containing one or more ether or hydroxy groups;

- 25 as enantiomers or mixture of diastereoisomers, and their pharmaceutically acceptable salts.

2. Compound according to Claim 1 wherein:

f is 1

m is 0

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, same or different are a group -CONR- and -NRCO-,

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Sub  
A2

R is H or methyl

R<sub>1</sub> and R<sub>2</sub> same or different, are:

-CH<sub>2</sub>-Ar wherein Ar is an aromatic group chosen among benzene, pyridine, indole, possibly substituted up to two residues with substituents chosen among:  
5 C<sub>1</sub>-3 alkyl and haloalkyl, C<sub>1</sub>-3 alkyloxy, C<sub>2</sub>-4 amino alkyloxy, halogens, OH, NH<sub>2</sub>, CN, NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, same or different, are H or C<sub>1</sub>-3 alkyl;

R<sub>3</sub> is

- CH<sub>2</sub>-Ar<sub>1</sub> wherein Ar<sub>1</sub> is an aromatic group chosen among: alfa naphthyl, beta naphthyl, phenyl, phenyl substituted up to two residues chosen among C<sub>1</sub>-3 alkyl  
10 and haloalkyl, C<sub>1</sub>-3 alkyloxy, halogens, OH, NH<sub>2</sub>,

R<sub>4</sub> is as defined in Claim 1.

3. Compounds according to Claim 2 wherein:

- X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub> are -CONR-,

R is H

15 - R<sub>1</sub> is the lateral chain of tryptophan;

- R<sub>2</sub> is the lateral chain of phenylalanine possibly substituted with up to two residues chosen among: chlorine, fluorine, CF<sub>3</sub>, OH, CN; or a group 3-pyridyl-methyl; or a group 4-pyridyl-methyl;

- R<sub>3</sub> is benzyl.

20 and f, m and R<sub>4</sub> are as defined in claim 2

4. Compounds according to claim 3 wherein:

R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, f, m are as above defined and:

R<sub>4</sub> is a group NR<sub>8</sub>R<sub>9</sub> wherein:

R<sub>8</sub> is H or methyl;

25 R<sub>9</sub> is a group chosen among: : 4-tetrahydropyranyl, 4-tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidiny, N-metansulfonyl-4-piperidiny, N-aminosulfonyl-4-piperidiny, or R<sub>8</sub> and R<sub>9</sub> together with the N atom to which they are linked represent: N-methyl-piperaziny, N-acetyl-piperaziny, piperaziny, N-methanesulfonyl-  
30 piperaziny

5. Compounds according to Claim 4 represented by:

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- i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 5 iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 10 vi) cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 15 viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 20 xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF<sub>3</sub>)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 25 xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}
- 30

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xvii) cyclo{Suc[1-(R)-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xviii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xix) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xx) cyclo{Suc[1-(R)-4-methanesulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

6. Compound according to Claim 3 wherein :

R<sub>4</sub> represents a group NR<sub>8</sub>R<sub>9</sub>, where R<sub>8</sub> is H and R<sub>9</sub> is chosen among: methanesulfonyl, tosyl, a group (CH<sub>2</sub>)<sub>g</sub>-R<sub>10</sub> wherein g is 1, 2 and R<sub>10</sub> is chosen among: morpholine, furan, CN.

and f, m, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined in claim 3

7. Compound according to claim 6 represented by:

xxi) cyclo{Suc[1-(S)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxii) cyclo{Suc[1-(R)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxiii) cyclo{Suc[1-(S)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxiv) cyclo{Suc[1-(R)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxvi) cyclo{Suc[1-(R)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxvii) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xxviii) cyclo{Suc[1-(R)-cyanomethylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-

CH<sub>2</sub>NH]]}

8. Compounds according to claim 3 wherein:

R<sub>4</sub> is a group - N(R<sub>11</sub>)CO(CH<sub>2</sub>)<sub>h</sub>-R<sub>12</sub> wherein R<sub>11</sub> is H, h is 0 or 1, and R<sub>12</sub> is chosen among: 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-aminosulfonyl-piperazine, 1-oxo-thiomorpholine, 4-hydroxy-cyclohexan-1-yl-amino and f, m, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined in claim 3

9. Compounds according to Claim 8 represented by:

- 10 xxix) cyclo{Suc[1-(R)-2-(4-morpholino)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxx) cyclo{Suc[1-(S)-2-(4-morpholino)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxxi) cyclo{Suc[1-(S)-2-(tetrazol-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- 15 xxxii) cyclo{Suc[1-(R)-2-(tetrazol-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxxiii) cyclo{Suc[1-(S)-2-(5-mercapto-tetrazol-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- 20 xxxiv) cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxxv) cyclo{Suc[1-(R)-2-(furanil)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxxvi) cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- 25 xxxvii) cyclo{Suc[1-(R)-2-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- xxxviii) cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]]}
- 30 xxxix) cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetyl-amino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub> AMENDED SHEET

xl) cyclo{Suc[1-(R)-2-(3-hydroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xli) cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

5 xlii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xliii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

10 xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xlvi) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xlvii) cyclo{Suc[1-(R)-2-(trans-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

15 10. Compounds according to Claim 3 wherein:

Sub 15/ R4 represents a group COR<sub>13</sub> wherein R<sub>13</sub> is a group chosen among morpholine and 4-(hydroxyethoxyethyl)-piperazine.

and f, m, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined in claim 3

11. Compounds according to claim 10 represented by:

20 xlviii) cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

xlix) cyclo{Suc[1-(4-hydroxyethoxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>)-CH<sub>2</sub>NH]}

Sub 16/ 25 12. Pharmaceutical compositions containing as active principle compounds of general formula (I) according to Claim 1 in combination with pharmaceutically acceptable carriers or excipients.

13. Pharmaceutical compositions according to Claim 12 for use as tachykinins antagonists.

30 14. Pharmaceutical compositions according to claim 13 for use as antagonists on human NK2 receptor .

15. Pharmaceutical compositions according to claim 14 for use in the treatment of

the bronchospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

16. Use of a compound according to Claim 1 as tachykinins antagonist

5 17. Use of a comound according to Claim 1 as NK-2 antagonist.

18. Use of a compound according to Claim 1 for the treatment of the bronchospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

10 19. Method for the treatment of the bronchospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections kidney colics wherein amounts of 0,1 - 10mg/ body weight of an active principle represented by compounds of formula (I) according to Claim 1 are administered to the patient.

Add  
A'

Add  
B'